to be rejoined when a claim generic thereto is found to be allowable, 37 C.F.R. § 1.141. Claims 19 - 21, 23 - 33, 39 - 40, 43, 45, 47, 49 - 55, and 61 - 63 have been examined and rejected. Claims 19, 31, and 32 are amended herein for reasons further described herein below.

Written Description "New Matter" Rejections

In a "new matter" rejection, the Examiner has rejected claims 19 - 21, 23 - 33, 39 - 40, 43, 45, 47, 49 - 55, and 61 - 63 under 35 U.S.C. § 112, first paragraph for lack of adequate written description of the phrase "MHC-dependent nominal antigen", arguing that "the specification supports only the terms MHC directed T cell responses and nominal antigens."[1]

Applicants respectfully traverse the rejection: "[i]f lack of literal support alone were enough to support a rejection under Section 112, then the statement of *In re Lukach* . . . that 'the invention claimed does not have to be described in *ipsis verbis* in order to satisfy the description requirement of Section 112,' is empty verbiage," *Union Oil Co. of California v. Atlantic Richfield Co.*, 54 USPQ2d 1227, 1235 (Fed. Cir. 2000).

Nonetheless, to expedite prosecution, applicants herein amend claims 19, 31 and 32 to delete the phrase "MHC-dependent"; since nominal antigens are by definition those that depend upon MHC presentation, the scope remains the same, the offending phrase has been deleted, and the rejection has been obviated. Applicants have also taken this opportunity to amend the preamble of claim 19 more particularly to point out and distinctly claim that the T

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[1] Office Action, p. 2.

cells to be detected in the claimed method are those that are specific for the nominal antigen.

Applicants respectfully submit that the rejection has been obviated and, accordingly, should be withdrawn.

Scope of Enablement Rejections

The Examiner has rejected claims 19 - 21, 23 - 33, 39 - 40, 43, 45, 47, 49 - 55 and 61 - 63 under 35 U.S.C. § 112, first paragraph, for inadequate scope of enablement.

Acknowledging that "the specification [is] . . . enabling for: a method of detecting antigen specific T lymphocytes, comprising: contacting a sample containing PBMC with an MHC-dependent nominal antigen and flow cytometrically detecting the intracellular binding of an anti-IL-2, anti-IFN-γ, or anti-TNF-α antibody,"[2] the Examiner argues that the specification nonetheless does not reasonably provide enablement commensurate in scope with applicant's claims, which call more broadly for "flow cytometrically detecting the intracellular binding of a cytokine-specific antibody."[3]

Applicants respectfully traverse the rejection and request reconsideration thereof.[4]

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[2] Applicants respectfully submit that claim 43, "wherein said cytokine-specific antibody is specific for γ-IFN," is thus free of, and is by inadvertence improperly included within, the stated rejection.

[3] Office Action, p. 3 (emphasis added).

[4] A prefatory comment is in order. The Examiner states that "[t]he specification discloses a method of intracellularly detecting only the cytokines IL-2, IFN-γ, or TNF-α." Office Action, p. 3 (emphasis added). While it is true that the specification's working examples are limited to intracellular detection of IL-2, IFN-γ, and TNF-α, the specification as a whole discloses that the method specifically includes intracellular detection of IL-4 (specification p. 5, line 2) and IL-13 (specification p. 8, line 18), and teaches more generally,

The Examiner grounds his rejection on the observation that certain "'antibodies that work well in detecting secreted cytokines may perform poorly in intracellular assays'". From this observation, the Examiner concludes "that the use of any particular anti-cytokine antibody is unpredictable," and reasons therefrom that the "unpredictability indicates that undue experimentation would be required to practice the invention."

Applicants disagree: notwithstanding the existence of antibodies that may prove inoperable in the claimed methods, it would not have required undue experimentation to identify antibodies that do work, and to distinguish such antibodies from those that cannot be used in applicants' claimed methods.

Indeed, in the very case cited by the Examiner in support of his rejection, the Court of Appeals for the Federal Circuit found that, although characteristics of any given antibody may be unpredictable, "undue experimentation would not be required" to find those that met the claim criteria,[5] because

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using broad language, that the method can be practiced by detecting "one or more intracellular cytokines" (specification p. 4, line 13). "The first paragraph of § 112 requires nothing more than objective enablement. How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance." *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971) (emphasis added).

[5] "Wands' disclosure provides considerable direction and guidance on how to practice their invention and presents working examples. There was a high level of skill in the art at the time when the application was filed, and all of the methods needed to practice the invention were well known.

The nature of monoclonal antibody technology is that it involves screening hybridomas to determine which ones secrete antibody with desired characteristics. Practitioners of this art are prepared to screen negative hybridomas in order to find one that makes the desired antibody. . . ." *In re Wands*, 8 USPQ2d 1400, 1406 (Fed. Cir. 1988) (emphasis added).

> enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is "undue," not "experimentation." The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art. The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.[6]

Applicants respectfully submit that the Examiner has failed to explain why the identification of anti-cytokine antibodies useful in applicants' invention would require anything more than routine screening, particularly in light of the Examiner's explicit acknowledgment that applicants have demonstrated that antibodies to TNF-α, IL-2, and γ-IFN are operable in the methods of the present invention.

Furthermore, although it is true that "'antibodies that work well in detecting secreted cytokines may perform poorly in intracellular assays'", by the time the present invention was made there had been a variety of antibodies, to a variety of cytokines, that had already been demonstrated to bind to cytokines within fixed and permeabilized lymphocytes.[7] The Examiner has advanced no

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[6] *In re Wands*, 8 USPQ2d at 1404 (internal citations and quotation marks omitted).

[7] Sander *et al.*, "Assessment of Cytokines by Immunofluorescence and the Paraformaldehye-Saponin Procedure," *Immunological Reviews* 119:65 - 93 (1991) (Exhibit 1 attached hereto); Sander *et al.*, "Similar frequencies and kinetics of cytokine producing cells in murine peripheral blood and spleen: cytokine detection by immunoassay and intracellular immunostaining," *J. Immunol. Methods* 166:201-214 (1993) (attached

reason why such antibodies should have occasioned unpredictable results in applicants' claimed methods; *a fortiori*, the Examiner has not explained why selection from among such antibodies of those that are operable in applicants' claimed methods should have occasioned undue experimentation.

Absent such explanations, the Examiner's *prima facie* case has failed, and applicants are not obliged to come forward with evidence in rebuttal.

Nonetheless, solely to expedite prosecution,[8] applicants previously filed the declaration of Dr. Calman Prussin, providing evidence that those skilled in the art, without undue experimentation, could readily have identified antibodies operable in applicants' claimed methods that are specific for cytokines other than those explicitly exemplified in applicants' specification.

In response, the Examiner dismisses the declaration as "insufficient".

With respect to the Examiner's comment that "Dr. Prussin['s] . . . Curriculum Vitae indicates no particular training in cellular immunology and only one relevant peer-reviewed publication,"[9] applicants offer the following response.

As pointed out in Dr. Prussin's declaration, there were three (3) groups that had published on the flow

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hereto as Exhibit 2); Andersson *et al.*, "Immunolabeling of cytokine-producing cells in tissues and in suspension," in Cytokine-Producing Cells (Les cellules productrices de cytokines), INSERM Atelier de Formation No. 63, 1994 (downloaded copy attached hereto as Exhibit 3).

[8] And without thereby admitting to the sufficiency of the Examiner's *prima facie* case under 35 U.S.C. § 112, first paragraph.

[9] Office Action , p. 4.

cytometric detection of intracellular cytokines in T lymphocytes before the priority date of the instant application: his, the instant inventors', and Dr. Jung's. Applicants submit that Dr. Prussin should thereby be counted as one among a small handful of scientists best able to speak knowledgeably to the Examiner's enablement concerns.

Applicants further submit that Dr. Prussin's ***two*** 1995 references on flow cytometric detection of intracellular cytokines (further described in Dr. Prussin's Declaration) have been cited 147 and 99 times since their respective publications (see the Science Citation Index® search output presented as Exhibits 4 and 5 to this response), a citation rate far greater than that of the average life science reference, evidence that those skilled in the art believe that Dr. Prussin's contributions to this art are significant.[10]

The Examiner further argues that "Dr. Prussin . . . merely asserts that the invention should work."[11]

This is surely not the case. In paragraph 39, Dr. Prussin describes how one skilled in the art would have

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[10] And applicants take this opportunity respectfully to commend to the Examiner's attention the unequivocal language with which the Federal Circuit disapproved another Examiner's summary dismissal of expert testimony:

> [w]e . . . hold that the examiner's final rejection and Answer contained two errors: (1) viewing the . . . declaration as opinion evidence addressing a question of law rather than a question of fact; and (2) the summary dismissal of the declaration, without an adequate explanation of why the declaration failed to rebut the Board's prima facie case [under 35 U.S.C.§ 112].

In re Alton, 37 USPQ2d 1578, 1582 (Fed. Cir. 1996).

[11] Office Action, p. 4.

identified cytokines, other than those specifically named in the present specification, that could serve as a signal of antigen-specific T cell stimulation; in paragraph 42, Dr. Prussin describes how antibody candidates specific for such cytokines would be tested.

Solely to expedite prosecution, however, applicants file concurrently herewith a second declaration by Dr. Prussin. Although applicants thank the Examiner for his suggestion, the declaration does not speak to "the differences between the conformations of secreted and intracellular cytokines"; rather, the declaration sets forth in greater detail how the skilled artisan would have screened antibodies for operability, and by reference to data from Dr. Prussin's own efforts, demonstrates that such routine screening would have been attended by a high probability of success.

Applicants respectfully submit that the declaratory evidence is sufficient to rebut any *prima facie* case that might ultimately be deemed established, and respectfully submit that the rejection is in error and should be withdrawn.

Written Description Rejection

Claims 19 - 21, 23 - 33, 40, 43, 45, 47, 49 - 55 and 61 - 63 are rejected for inadequate written description under 35 U.S.C. § 112, first paragraph, of "inhibitor[s] of cytokine secretion" other than brefeldin A (BFA).[12] Applicants respectfully disagree: one skilled in the art would have recognized that applicants were in possession of

[12] Claim 39, drawn to the method of claim 19 "wherein said inhibitor of cytokine secretion is Brefeldin A," is excluded from the rejection.

the claimed methods as practiced with either BFA or with monensin.

As noted in the first-filed Declaration of Dr. Calman Prussin, Jung and colleagues pioneered the use of flow cytometry for detecting cytokine production at the single cell level in peripheral blood mononuclear cells ("PBMC").[13] In the Jung *et al.* method, PBMC are stimulated with a polyclonal stimulus, PMA+I, in the presence of monensin, an inhibitor of the Golgi-mediated secretion pathway. In both May[14] and December[15] 1995, Dr. Prussin published papers describing an improvement on the Jung *et al.* method, again using monensin as inhibitor of Golgi-mediated secretion. Between the May and December publications of the Prussin work, Picker *et al.*[16] published similar work, for the first time substituting BFA for monensin as an inhibitor of Golgi-mediated secretion.

Thus, it is clear that the skilled artisan would reasonably have believed that applicants, in describing use of "an agent which blocks the secretion of such

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[13] Jung *et al.*, "Detection of intracellular cytokines by flow cytometry," *J. Immunol. Methods* 159:197-207 (1993) (attached to Dr. Prussin's first-filed declaration).

[14] Elson *et al.*, "Flow cytometric analysis for cytokine production identifies T helper 1, T helper 2, and T helper 0 cells within the human $CD4^{+}CD27^{-}$ lymphocyte subpopulation," *J. Immunol.* 154(9):4294-4301 (May 1, 1995) (attached to Dr. Prussin's earlier-filed declaration).

[15] Prussin *et al.*, "Detection of intracytoplasmic cytokine using flow cytometry and directly conjugated anti-cytokine antibodies," *J. Immunol. Methods* 188:117-128 (1995) (attached to Dr. Prussin's first declaration).

[16] Picker *et al.*, "Direct Demonstration of Cytokine Synthesis Heterogeneity Among Human Memory/Effector T Cells by Flow Cytometry," *Blood* 86:1408-1419 (August 15, 1995) (of record).

intracellular cytokines"[17], an "inhibitor of intracellular transport which prevents secretion of any produced cytokines", the preferred embodiment of which is Brefeldin A[18], were in possession of a method in which the "inhibitor of cytokine secretion" was not limited to brefeldin A.

Priority

The Examiner denies applicants' priority claim to application no. 08/760,447, filed December 6, 1996, now abandoned. Applicants respectfully traverse the denial and request reconsideration.

The Examiner argues that, in contrast to the instant application, "the '447 application discloses and claims methods of assessing T cells within a population" whereas, "[i]n contrast, the instant application discloses and claims a method of detecting individual T cells that respond to a[] . . . nominal antigen."[19]

That is simply incorrect: each and every dot on the 35 dot plots presented in FIGS. 1 - 4 of the '447 application represents a single cell that has been individually queried by the flow cytometer's laser. When the '447 specification says that "48,000 events, gated on viable CD4+ lymphocytes, are shown in each plot,"[20] the

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17 Specification p. 6, lines 2 - 3.

18 Specification p. 6, line 5.

19 Office action p. 5, emphasis in the original.

20 '447 specification p. 5, lines 4- 5; p. 5, line 18; p. 6, line 6; p. 6, lines 22 - 23.

"events" of which the specification speaks are individually queried and characterized $CD4^+$ T cells.[21]

The Examiner further states that the priority document discloses no "MHC-dependent nominal viral antigens" as claimed in the instant application. That too is incorrect. FIGS. 1 - 5 of the '447 application specifically exemplify T cell response to cytomegalo**virus** antigen; these viral antigens[22] are nominal antigens, that is, are neither superantigens nor polyclonal mitogens, thus requiring specific presentation by MHC.

The Examiner then argues that "[e]ven the critical parameter, the length of the assay, is unclear in the parent application. While one figure indicates a 6 hour assay, the preferred embodiment (page 3) discloses a 101.5 hour incubation."[23] Again, applicants traverse the ground for rejecting the priority claim.

First, applicants are aware of no legal authority that permits the Examiner to assert *sua sponte* that an element that appears solely in certain dependent claims (here, claims 54 and 55) is "critical" to all of applicants' claims.[24] The sole question presented is whether the '447

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[21] The figures thus present data on 35 x 48,000 = 1,680,000 individual T lymphocytes.

[22] And the '447 specification discloses more broadly the applicability of the described methods to "viral antigens" in general ('447 specification p. 3, lines 3 - 5).

[23] Office Action, p. 5.

[24] Indeed, with respect to rejections under § 112, first paragraph, the M.P.E.P. admonishes that

> [a]n enablement rejection based on the grounds that a disclosed critical limitation is missing from a claim **should be made only when** the language of **the specification makes it clear** that the limitation is critical for the invention to function as intended. Broad language in the disclosure, including the

specification provides enabling written description for applicants' invention **as claimed**. Applicants maintain that it does.

Second, the Examiner is wrong on the facts. The '447 application clearly discloses antigen incubations of 6 - 24 hours (providing explicit written description and enabling support for present claims 54 and 55). Thus, "this invention provides an assay protocol using peripheral blood mononuclear cells . . . for the rapid (generally less than 24 hours, preferably less than 6 hours), highly efficient, Ag-specific activation of secretion-inhibited CD4+ . . . T cells. . . . "[25] To similar effect, see '447 specification p. 6, lines 2 - 5; p. 8, lines 22 - 23; p. 9, line 36 - p. 10, line 3; '447 application original claims 9 and 10. It is no moment that the '447 application additionally describes longer incubations.[26]

Applicants submit that the '447 specification meets the requirements of § 112, ¶ 1, and thus the requirements of 35 U.S.C. § 120, and that the denial of priority claim is in error and should be withdrawn.

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abstract, omitting an allegedly critical feature, tends to rebut the argument of criticality.

M.P.E.P. § 2164.08(c), 7th ed., Rev. 1, Feb. 2000 (emphasis added). Nowhere in the specification of the instant application have applicants suggested that the duration of incubation with antigen is a "critical parameter". Having explicitly presented claims broad thereto, applicants have in fact rebutted the argument of criticality.

[25] '447 specification, p. 2, lines 30 - 33.

[26] And as to that longer incubation, applicants respectfully suggest that the skilled artisan would readily have understood that the "101.5 hr" incubation is a typographical error and should properly have read "1 - 1.5 hr".

Obviousness Rejections under 35 U.S.C. § 103

The Examiner rejects claims 19 - 21, 23 - 33, 39 - 40, 43, 45, 47, 49 - 55 and 61 - 53 under 35 U.S.C. § 103(a) as being unpatentable over Becton Dickinson Application Note 1 ("Detection of Intracellular Cytokines in Activated Lymphocytes") in view of Maino *et al.* (FastImmune™ Assay System) and U.S. Patent No. 6,143,299 (the "'299 patent"). Applicants respectfully traverse the rejection.

To begin, applicants respectfully submit that **Application Note 1 is not available as a reference** as against applicants' claims which, as discussed at length above, are entitled to the December 6, 1996 filing date of parent application no. 08/760,447: as evidenced by the Becton Dickinson "NewsFlash" attached hereto as Exhibit 6, the FastImmune Cytokine Application Note #1 was first made "available for distribution" to the public on December 19, 1996. Accordingly, the Examiner's *prima facie* case of obviousness is in error and the rejection must be withdrawn.

Even were Application Note 1 available as a reference, applicants submit that the rejection is in error and should be withdrawn.

Application Note 1 describes the use of polyclonal stimuli - such as PMA+I, or superantigens such as Staphylococcal enterotoxin B (SEB) – to activate large subsets of T lymphocytes present in peripheral blood samples, with activation thereafter assessed by detection of intracellular cytokine production in the activated subset. Application Note 1 thus describes no more than Picker *et al.*[27] Rejections over Picker *et al.* having been withdrawn "[i]n view of Applicant's amendment and declarations",

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[27] Picker *et al.*, *Blood* 86:1408 - 1419 (1995) (of record).

applicants respectfully submit that the present rejection should equally be withdrawn, and for the identical reasons.

Briefly to summarize those reasons, further described in the earlier-filed Declarations of Dr. John Altman and Calman Prussin, after the "**fully activating stimulus**"[28] by polyclonal mitogen (PMA+I),[29] Picker *et al.* observed that only **2.5**% of $CD8^-$ lymphocytes, and only **0.8**% of $CD8^+$ cells, could be shown to express IL-4. Analogously, after stimulation of **20.9**% of $CD4^+$ cells by superantigen, only **1.8**% of the $CD69^+CD4^+$ cells could be shown to express IL-4 (Picker Fig. 3). IL-2 and γ-IFN were produced in a higher percentage, but still only in a subset of the activated T cells.

Polyclonal mitogens and bacterial superantigens were well known to stimulate a far greater percentage of T lymphocytes than do MHC-dependent nominal antigens: prior art assays, such as limiting dilution assays ("LDA") and ELISPOT, had taught that the percentage of T cells that would respond to nominal antigen would be far lower, perhaps orders of magnitude lower. For example, in the Lolli *et al.* reference cited by the Examiner, which seems representative of ELISPOT reports in the art of the time, the median frequency of antigen-specific T cells is reported to be on the order of 0.01% of PBMC (about 1/20,000 to 1/6,000 blood cells).

It was reasonable, therefore, for the person of ordinary skill in immunology, upon reading the Picker *et al.* paper (or Application Note 1, which cites to Picker *et al.*),

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[28] Picker *et al.*, page 1417, col. 1.

[29] Picker *et al.*'s figure 1 shows that, after 4 hours' incubation with PMA+I and Brefeldin A (BFA), fully **94.7**% of $CD8^-$ (that is, $CD4^+$ cells) become $CD69^+$, indicating activation; Picker *et al.*'s figure 1 further shows that **96.4**% of $CD8^+$ lymphocytes become $CD69^+$ after incubation with PMA+I and BFA.

to assume that the frequency of antigen-specific cells would be far too low in a freshly drawn, unexpanded, whole blood sample of reasonable size for reliable detection by the intracellular cytokine method.

Furthermore, the expected frequency of antigen-specific cells was expected to fall below the level of noise in the flow cytometric intracellular cytokine assay.

Looking at the middle panel of the top row of Picker *et al.*'s Figure 1 (page 1410), fully 0.7% of $CD8^-$ ($CD4^+$) cells and 1.1% of $CD8^+$ cells give a positive signal for IL-2 (middle panel), **even without stimulation**. Looking at gamma interferon (right-most of the Picker *et al.* FIG. 1 panels), fully 0.8% of unstimulated $CD8^-$ ($CD4^+$) cells give a positive signal for γ-IFN, even without stimulation. This is a measure of noise in the Picker *et al.* system; in order to be detected reliably using the Picker *et al.* technique, a true event would need to be present in greater than about 1% of $CD4^+$ or $CD8^+$ T cells.

As noted above, the art had taught, however, that the percentage of antigen-specific T cells would be far below this level.

Thus, the Picker *et al.* disclosure itself, consistent with prior art data, such as those presented by Lolli *et al.*,[30] taught away from successful modification of the Picker technique to detection of antigen-specific T cells, suggesting that too few antigen-specific events would be present to permit their ready and reliable detection. And for the same reason, Picker *et al.* and Lolli *et al.* would have suggested that adapting the flow cytometric intracellular cytokine method to detection of antigen-

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[30] Lolli *et al.*, *FEMS Immun. Med. Microbiol.* 7:55-62 (1993) and Lolli *et al.*, *AIDS Res. Human Retroviruses* 10:115 - 120 (1994), both previously made of record.

specific T lymphocytes would have failed, the antithesis of a "reasonable expectation of success".

Double Patenting

The Examiner provisionally rejects various claims[31] of the present application for obviousness-type double patenting over claims of copending application no. 09/526,253, notwithstanding the restriction requirement issued therein. In the interests of expediting prosecution, applicants hereby formally traverse the rejection, but defer substantive argument until such time as the provisional rejection is rendered nonprovisional by allowance of subject matter in the '253 application.

CONCLUSION

Applicants submit that the remarks set forth herein and the evidence filed concurrently herewith place the claims in good and proper form for allowance. If the Examiner believes, however, that the amendments, arguments, and evidence are in any way insufficient to warrant allowance of all pending claims, applicants believe that the time is appropriate for a personal or telephonic interview. At the interview, applicants would propose to discuss the present application and any of the three copending divisional applications for which matters remain

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[31] The rejection as stated appears to have a clerical error, inasmuch as none of claims "1 - 8, 10 - 15, [or] 17" are pending in the present application. Based upon the corresponding rejection in the '253 application, applicants believe that the Examiner intended to levy the rejection against claims 19 - 55 and 61 - 63 of the present application, but respectfully request clarification.

outstanding. Accordingly, applicants hereby formally request that, should any matters be unresolved, the Examiner **call the undersigned to set a time for personal or telephonic interview**.

Respectfully submitted,

30 JULY 2001

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Attachments:

- Exhibit 1 — Sander *et al.*, *Immunological Reviews* 119:65 - 93 (1991)
- Exhibit 2 — Sander *et al.*, *J. Immunol. Methods* 166:201-214 (1993)
- Exhibit 3 — Andersson *et al.*, INSERM Atelier de Formation No. 63, 1994 (downloaded copy)
- Exhibit 4 — Science Citation Index® search output, query: Cited Reference = Prussin, J. Immunol. Methods 188:117 (1995)

- Exhibit 5 — Science Citation Index® search output, query: Cited Reference = Elson, J. Immunol. 154:4294 (1995)

- Exhibit 6 — Internal Becton Dickinson NewsFlash

Enclosure

- Second Declaration of Dr. Calman Prussin Under 37 C.F.R. § 1.132

Appendix Pursuant to 37 C.F.R. § 1.121(c)(1)(ii)

19 (twice amended). A method of detecting [antigen-specific] T lymphocytes that are specific for a nominal antigen, comprising:

contacting a sample containing peripheral blood mononuclear cells with a [an MHC-dependent] nominal antigen;

adding to said sample an inhibitor of cytokine secretion;

adding to said sample at least one cytokine-specific antibody and at least one T lymphocyte subset-defining antibody; and then

flow cytometrically detecting the intracellular binding of said cytokine-specific antibody by cells in the defined T lymphocyte subset.

31 (once amended). The method of claim 19, wherein said [MHC-dependent] nominal antigen is selected from the group consisting of alloantigens, viral antigens, autoantigens, viral antigens, and bacterial antigens.

32 (once amended). The method of claim 31, wherein said [MHC-dependent] nominal antigen is a viral antigen.